

# Individualized dosing with axitinib: rationale and practical guidance

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Axitinib is a potent, selective, vascular endothelial growth factor receptor inhibitor with demonstrated efficacy as second-line treatment for metastatic renal cell carcinoma. Analyses of axitinib drug exposures have demonstrated high interpatient variability in patients receiving the 5 mg twice-daily (b.i.d.) starting dose. Clinical criteria can be used to assess whether individual patients may benefit further from dose modifications, based on their safety and tolerability data. This review provides practical guidance on the 'flexible dosing' method, to help physicians identify who would benefit from dose escalations, dose reductions or continuation with manageable toxicity at the 5 mg b.i.d. dose. This flexible approach allows patients to achieve the best possible outcomes without compromising safety.

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## Rationale for individualized dosing

Before the development of molecular targeted therapy, most available anticancer drugs, with hormone therapies and immunotherapies being notable exceptions, were chemotherapy agents: chemicals aimed at having a cytotoxic effect on cancer cells [1,2]. These drugs were dosed according to a patient's weight or body surface area, based on the observation that patients with a greater body size generally have a greater volume of distribution and require higher doses than smaller patients to reach equal drug concentrations [3]. It was thought this approach would deliver consistent systemic drug exposure, thereby optimizing treatment outcomes. This dosing approach was also chosen based on a lack of a better option at that time. However, it was known that multiple factors beyond patient size (including age, sex, renal function, hepatic function, concomitant medication, disease state and genetics) could have an impact on the actual concentration of a drug in an individual's bloodstream [4]. Consequently, there remains high variability between patients (interpatient variability) in systemic drug concentrations, even when normalized for weight/body surface area [5].

When molecular targeted agents were first introduced for use in metastatic renal cell carcinoma (mRCC), these drugs were recommended at a fixed dose, based on an assumption that the maximum tolerated fixed dose would result in the best efficacy and that this same high dose would be appropriate for all patients. However, most tyrosine kinase inhibitors (TKIs) demonstrate high interpatient variability in drug exposure (depending on oral bioavailability and first-pass liver metabolism of drugs); therefore, the subsequent therapeutic effect and toxicity for the same administered dose may vary [6]. As a result, fixed dosing may result in suboptimal efficacy for some patients or excessive toxicity in others [7]. In addition, higher-than-needed doses may be excessive if therapeutic effects are already achieved at lower doses.

Table 1. The half-life, starting dose and schedule of oral targeted metastatic renal cell carcinoma drugs.			
Drug name	Half-life (h)	Starting dose	Schedule
Sunitinib	40–60 (80–110 [active metabolite])	50 mg	Once-daily dosing
Pazopanib	30.9	800 mg	Once-daily dosing
Sorafenib	25–48	400 mg	Twice-daily dosing <sup>†</sup>
Everolimus	30	10 mg	Once-daily dosing
Cabozantinib	~99	60 mg	Once-daily dosing
Lenvatinib	~28	18 mg	Once-daily dosing <sup>‡</sup>
Axitinib	2.5–6.1	5 mg	Twice-daily dosing

Data taken from [13–19].

<sup>†</sup>Sorafenib is dosed twice-daily, despite having a half-life ranging from 25 to 48 h. This is because of its low bioavailability.

<sup>‡</sup>In combination with everolimus 5 mg once-daily. The daily doses of lenvatinib and, if necessary, everolimus are to be modified as needed according to the dose/toxicity management plan.

It is therefore apparent that neither the weight/body surface area-based approach nor the fixed-dosing approach is sufficient to account for interpatient variability, and a more flexible, individualized method (to find the optimal dose for an individual patient) should be employed in some therapeutic scenarios [5,8]. If not, there is a risk that the patient will have suboptimal treatment outcomes due to either excessive toxicity or inadequate drug exposure [9]. Given the noncurative nature of these agents, it is important that a balance is reached to allow us to carefully optimize efficacy while managing adverse effects.

Axitinib is a potent, selective, second-generation VEGFR inhibitor with demonstrated efficacy as second-line treatment for mRCC [9,10]. Analyses of drug exposures in patients receiving the 5 mg twice-daily (b.i.d.) starting dose of axitinib have demonstrated high interpatient variability [8].

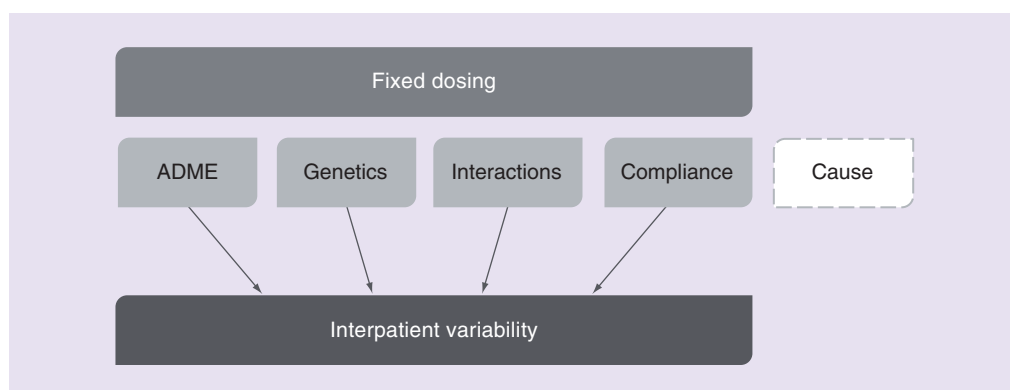
This review explores how the properties of axitinib contribute to its dosing profile and provides the rationale for why a flexible dosing method, based on individual safety and tolerability, gives us the opportunity to account for interpatient variability. Practical clinical guidance is also offered to help physicians individualize the axitinib dose and achieve the best possible outcomes for every patient.

How the dosing schedule & starting dose of axitinib were determined

All drugs have different properties, resulting in different doses and schedules that are determined during the clinical development program for each drug (Table 1). The half-life of a drug (defined as the time taken for the plasma drug concentration to reduce from peak concentration by half) is a key factor that helps inform how often a drug needs to be dosed [11,12]. As repeated doses are administered, the plasma concentration will usually build up and reach steady state, a concentration level that should be in the therapeutic range, for as long as regular doses are administered to balance the amount of drug being cleared [11]. The plasma half-life of axitinib ranges from 2.5 to 6.1 h; steady state is expected within 2–3 days of the initial dose and is maintained by b.i.d. dosing. B.i.d. dosing allows the therapeutic levels of axitinib to be maintained constantly when taken approximately 12 h apart [13]. As such, it is not necessary to administer axitinib more than twice daily. However, owing to the short half-life of axitinib, it is not appropriate to alter the schedule to once-daily; doing this would compromise the efficacy of axitinib because plasma concentrations would fall below therapeutic levels.

The maximum tolerated dose – that is, the dose immediately below that which causes dose-limiting toxicity according to a predefined threshold – was determined for axitinib in a Phase I trial of patients with various advanced solid malignancies [20]. 36 patients received fixed doses (5–30 mg b.i.d.) of axitinib in 28-day cycles; the maximum tolerated dose and recommended dose to be taken into Phase II and III trials was 5 mg b.i.d. The tolerability of this dose was confirmed in a large Phase III study (AXIS), in which the 5 mg b.i.d. starting dose was used [10].

Although the appropriate starting dose of axitinib is 5 mg b.i.d., this nonindividualized fixed dose does not take into account interpatient variability. Therefore, it is important that after initiation at 5 mg b.i.d., clinical criteria are used to guide whether the patient would benefit from a dose adjustment; these criteria are described in a later section of this review. First, however, it is important to understand why interpatient variability exists and why we need to account for it.



**Figure 1. Factors that can lead to interpatient variability in drug exposure.**

ADME: Absorption, distribution, metabolism, elimination.

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## Interpatient variability in axitinib exposure

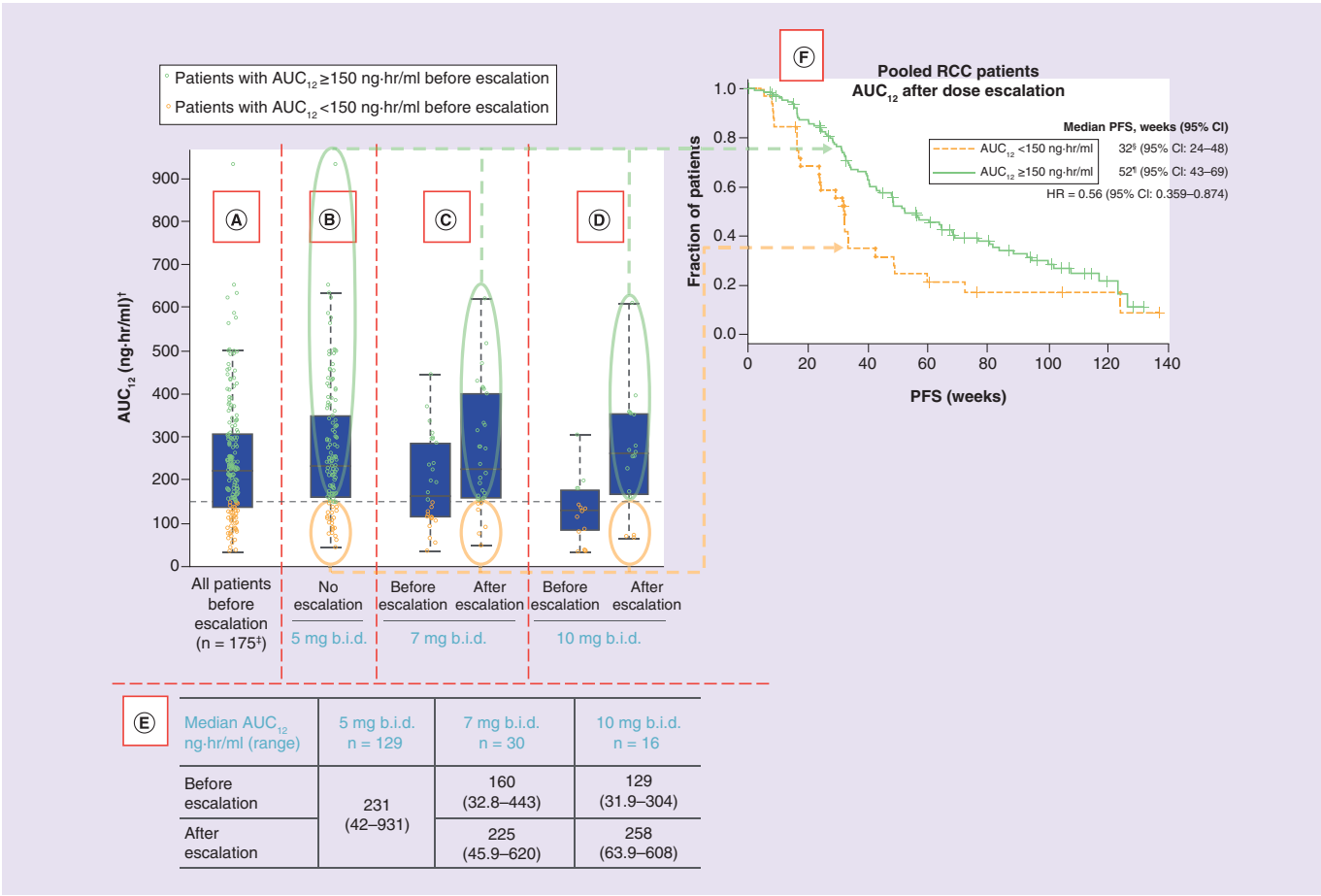
### Factors affecting drug exposure

A number of factors and metabolic processes in the body affect drug exposure. As can be expected, these factors are not the same in every patient, and there can also be differences in the impact of metabolic processes on exposure in an individual patient (Figure 1) [21,22]. For example, absorption, distribution, metabolism and elimination (ADME) all influence drug exposure [4]. After oral administration, axitinib shows a variable rate of absorption, reaching peak concentrations in plasma within 4 h [13,23]. Results from *in vitro* studies have demonstrated that axitinib is highly protein bound (>99%), mostly to albumin, with moderate binding to  $\alpha_1$ -acid glycoprotein [13,24]. Metabolism of axitinib is primarily performed by CYP3A4/5 in the liver and, to a lesser extent, by CYP1A2, CYP2C19 and UDP glucuronosyltransferase 1 family polypeptide A1 (UGT1A1) [13,24]. The main metabolites of axitinib are inactive [20,24]. Approximately 30–60% of orally administered axitinib is eliminated in the feces, with a further 23% eliminated renally [13]. Variability between patients in each of the four ADME processes has a direct impact on drug exposure and helps to explain why giving a fixed standard dose of a drug to all patients will not always produce either the same anticancer effect or the same side effects [7,21]. In addition, most drug-metabolizing enzymes are polymorphic; therefore, a patient's response to treatment can be affected by genetic variation [21]. Other factors affecting drug exposure include interactions with co-administered drugs that can lead to variation in plasma concentrations; the importance of drug–drug interactions on the safety profile of axitinib should be evaluated on an individual basis and physicians should be aware of the most common drug–drug interactions (Supplementary Table 1) [25]. Co-administration of axitinib with agents known to be strong CYP3A4/5 inhibitors (e.g., ketoconazole and clarithromycin) or inducers (e.g., phenytoin, dexamethasone, rifampicin and St John's wort) may cause axitinib plasma concentrations to increase or decrease, respectively [26].

Furthermore, for self-administered, oral regimens, compliance is an essential factor in determining efficacy. If a patient has poor compliance, this can impact on drug exposure and can be another factor that contributes to variability [27]. Notably, nearly all patients receiving axitinib for renal cancer will have previously received an alternative TKI – most likely according to a once-daily and (in the case of sunitinib) intermittent dosing schedule. Therefore, it is essential that patients clearly understand the dosing schedule for axitinib before commencing this treatment.

### Variability in exposure in patients given a standard dose of axitinib 5 mg b.i.d.

In a retrospective analysis of pooled data [8] (two Phase II studies in which axitinib was evaluated in cytokine-refractory mRCC [n = 116] [28,29] and one Phase II study in which axitinib was evaluated in sorafenib-refractory mRCC [n = 62] [30]), variability in axitinib exposure (as measured by the area under the plasma concentration–time curve [AUC]) was demonstrated in patients after they each received the same standard dose of 5 mg b.i.d.; Figure 2A shows the extent to which variations occurred between patients. Variations in axitinib exposure (expressed as coefficient of variation of up to 94%) have been previously reported; this variability in exposure is not unique to axitinib and similar variations can also be demonstrated with all other oral mRCC drugs [21,22].



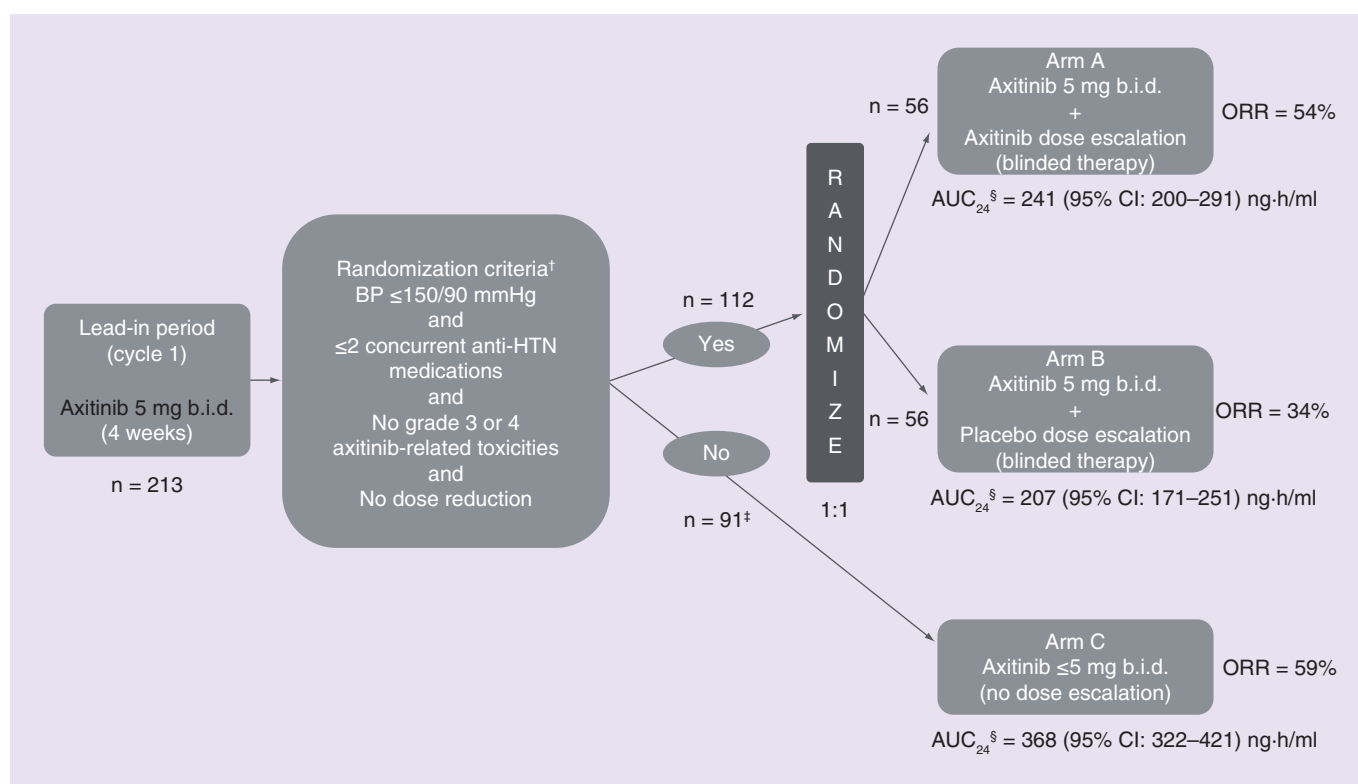
**Figure 2. Variability in exposure (as measured by area under the plasma concentration–time curve) in patients given a standard dose of axitinib 5 mg b.i.d.** Individual patients’ exposure levels: **(A)** all patients; **(B)** patients who remained on axitinib 5 mg b.i.d.; **(C)** before and after dose escalation to axitinib 7 mg b.i.d.; **(D)** before and after dose escalation to axitinib 10 mg b.i.d. **(E)** Median axitinib exposure levels in **(B)** to **(D)**. **(F)** Patients who can achieve a higher axitinib exposure have a better clinical outcome [8]. The central boxes represent the values ranging from the lower to the upper quartile (25th–75th percentile); the middle line of each box represents the median. Each dot represents an individual patient’s exposure level.

<sup>†</sup>Exposure (as measured by AUC) at the end of 4 weeks of study treatment.  
<sup>‡</sup>Three enrolled patients were not included in the analysis because of lack of dose-time data or only one measurable axitinib concentration [30].  
<sup>§</sup>36 patients met the AUC criterion; 26 PFS events were assessed by the investigator.  
<sup>¶</sup>139 patients met the AUC criterion; 83 PFS events were assessed by the investigator.  
AUC: Area under the plasma concentration–time curve; AUC<sub>12</sub>: Area under the plasma concentration–time curve from 0 to 12 h; b.i.d.: Twice-daily; CI: Confidence interval; HR: Hazard ratio; PFS: Progression-free survival; RCC: Renal cell carcinoma.

Because of the interpatient variability in half-life and exposure seen with axitinib, it is not possible to predict the exact exposure level a patient will have. However, Rini *et al.* demonstrated that increasing the axitinib dose leads to increased exposure [9]. Patients who, based on tolerability criteria, were eligible for subsequent dose escalation up to 7 mg b.i.d. (Figure 2C) and then 10 mg b.i.d. (Figure 2D) had lower median axitinib exposure to begin with at 5 mg b.i.d. than patients who were not eligible for dose escalation (Figure 2B). After dose escalation, median axitinib exposure increased to similar levels as those for patients who were not eligible for dose escalation (Figure 2E). These pharmacokinetic (PK) data confirm that exposure can be increased (via a dose escalation) in patients who are able to tolerate it.

Interpatient variability in drug exposure translates into variability in efficacy

An analysis of pooled data from these three Phase II studies found significant associations between axitinib exposure and efficacy outcomes [31]. In this population PK analysis (n = 178) assessing data from 168 patients



**Figure 3. Design of the Phase II 1046 study, baseline axitinib exposure levels and objective response rate by study group .**

†For at least two consecutive weeks.

‡Ten patients withdrew during the lead-in period.

§Subset of 73 patients with serial 6-h pharmacokinetic sampling, mean AUC<sub>24</sub> prior to randomization.

AUC<sub>24</sub>: Area under the plasma concentration–time curve from 0 to 24 h; b.i.d.: Twice-daily; BP: Blood pressure; CI: Confidence interval; HTN: Hypertension; ORR: Objective response rate.

with mRCC for whom data were available, the median (range) axitinib exposure at the end of 4 weeks of study treatment at 5 mg b.i.d. was 375 ng·h/ml (32.8–1728 ng·h/ml) [31]. Logistic regression analysis found a significant relationship between axitinib exposure and the probability of response (Response Evaluation Criteria in Solid Tumors [RECIST]-based objective responses [OR]) in these patients ( $p < 0.0001$ ); this translated into a 1.5-fold increase in the probability of achieving a partial response for every 100 ng·h/ml increase in AUC (Pfizer Ltd, Walton Oaks, Surrey, UK, data on file) [31]. Data from this analysis were also used to explore the relationship between AUC and the time-to-event endpoints of progression-free survival (PFS) and overall survival (OS). Univariate Cox proportional regression analysis was performed using exposure (as measured by AUC) as both a categorical and continuous variable; patients were stratified by AUC  $\geq 300$  ng·h/ml (high AUC) or  $< 300$  ng·h/ml (low AUC) [31]. The 300 ng·h/ml cut-off used in the analysis was determined based on data from Liu *et al.* [32] (total daily AUC, which correlated with the maximum reduction in blood flow and permeability, was determined to be reached at  $\sim 300$  ng·h/ml). Median PFS and OS were significantly longer in the high-AUC group versus the low-AUC group (13.8 vs 7.4 months [ $p = 0.003$ ] and 37.4 vs 15.8 months [ $p < 0.001$ ], respectively). When AUC was assessed as a continuous variable (any value between the minimum value and maximum value), the result was more significant than when using the 300 ng·h/ml cut-off; for PFS and OS, the hazard ratio [HR] was 0.871 ( $p = 0.001$ ) and 0.810 ( $p < 0.001$ ), respectively, for every 100 ng·h/ml increase in AUC [31]. These results demonstrate significant associations between exposure and clinical response for axitinib (i.e., patients with lower exposure are likely to receive less benefit than patients with higher exposure). Furthermore, as shown in Figure 2F, even after dose optimization, patients who achieve a higher axitinib exposure seem to have a better clinical outcome; these positive associations were further confirmed using data from the Phase II 1046 study [8]. Treatment-naïve patients with mRCC received axitinib 5 mg b.i.d. (Figure 3 [8,9]). At the end of a 4-week lead-in period, patients with no  $>$  Grade 2 treatment-related adverse events (AEs), no dose reduction, blood pressure (BP)  $\leq 150/90$  mmHg



and  $\leq 2$  antihypertensive drugs, for two consecutive weeks were randomly assigned (1:1) to either axitinib (Arm A) or placebo (Arm B) dose escalation. Patients who did not meet the aforementioned criteria and were therefore deemed not to require dose escalation continued at  $\leq 5$  mg b.i.d. (Arm C). It is worth noting that, using these criteria, approximately half of all patients included in the study were identified as potential candidates for dose escalation. The primary objective was to compare the proportion of patients achieving an OR between randomized groups. Axitinib dose escalation significantly improved drug exposure and, as a consequence, objective response rate (ORR), compared with placebo dose escalation: 30 patients (54%; 95% confidence interval [CI]: 40–67) versus 19 patients (34%; 95% CI: 22–48) in the axitinib and placebo dose-escalation groups, respectively, achieved an OR (risk ratio: 1.58 [95% CI: 1.02–2.45]; one-sided;  $p = 0.019$ ) [9]. In the nonrandomized group, 54 (59%; 95% CI: 49–70) patients had an OR, suggesting that patient selection criteria based on tolerability correctly indicated which patients had adequate axitinib exposure levels at 5 mg b.i.d. or below, and therefore did not require dose escalation. Decreasing tumor mass is not only a sign of efficacy but may bring clinical benefit in terms of symptom relief (e.g., pain caused by metastases or paraneoplastic syndromes such as hypercalcemia). The HR for PFS, a secondary endpoint in this trial, favored the axitinib dose-escalation group versus the placebo dose-escalation group (HR: 0.85; 95% CI: 0.54–1.35) but was not statistically significant (one-sided;  $p = 0.24$ ) [8,9]. OS data, which were not available at the time of the original analysis, demonstrated that the corresponding increase in drug exposure in axitinib-escalated patients also translated into a trend toward improvement in OS compared with patients who were eligible for dose escalation but who were placebo escalated (median OS was 42.7 months [95% CI: 24.7–not estimable] for axitinib escalation vs 30.4 months [95% CI: 23.7–45.0] for placebo escalation); the improvement in this secondary endpoint did not reach statistical significance (HR: 0.79; 95% CI: 0.49–1.27) [33]. Both the PFS and OS secondary endpoints had limited power to reach statistical significance in this Phase II trial [9,33].

### How can we address interpatient variability?

As has been described, there is interpatient variability in drug exposure with axitinib and increasing the dose, where tolerated, leads to an increase in exposure. Although there is a broad correlation between axitinib exposure and clinical benefit, there is no universal threshold above which response is guaranteed, reinforcing the importance of adjusting the dose (and therefore the exposure) to find an optimal balance between efficacy and tolerability. To address this, alternatives to fixed-dosing regimens have been explored; however, as outlined below, many of these methods are not currently feasible for axitinib.

### Therapeutic drug monitoring

Therapeutic drug monitoring is a technique whereby plasma drug concentrations are measured to individualize the dose given to a patient and achieve a target blood concentration; it is a technique used with some anticonvulsants and antibiotics (e.g., gentamicin) [21,34]. Given the expected variations among axitinib-treated patients, and the absence of a universal ‘active’ target exposure level, scheduled PK measurements (e.g., maximum plasma concentration and AUC) in individual patients for the purpose of guiding axitinib dosing are not performed in routine clinical practice. Furthermore, the properties of the drug itself mean there are inherent difficulties when measuring plasma concentrations; owing to the short half-life, axitinib concentrations rise and fall significantly during a dosing interval and there is minimal accumulation at steady state [13] (i.e., a concentration level that is therapeutically effective as long as regular doses are administered). In addition, axitinib degrades in the presence of light [35]; this could result in artefactual readings and the physician prescribing an incorrectly high dose of axitinib to the patient with resulting safety implications. With these limitations in mind, however, PK measurements could be considered on an individual basis, and only after checking the patient’s level of compliance with treatment.

### Phenotype-/genotype-guided dosing

Phenotype-guided dosing is based on the ability of an individual to process a drug according to phenotype (i.e., an individual’s enzymatic capability). For example, the midazolam clearance test assesses CYP3A activity and midazolam has been shown to be a good predictor of exposure to other CYP3A4 substrates, such as gefitinib [36]. Genotype-guided dosing is based on an individual’s genetic make-up and single nucleotide polymorphisms within their drug disposition genes (e.g., genes encoding for drug-metabolizing enzymes, efflux transporters and drug targets) [21]. Genetic variation in the therapeutic target may also define variability in efficacy. There are currently no validated genetic biomarkers available to guide dosing in axitinib patients; in a meta-analysis using pooled data from

11 healthy volunteer clinical pharmacology trials, no polymorphisms in a number of drug-metabolizing enzymes or transporters were found to be predictors of axitinib PK variability [37].

### Toxicity-adjusted dosing

Toxicity-adjusted dosing is based on the theory that specific toxicities are dependent, at least in part, on drug exposure. AEs can therefore be used to guide dosing and to achieve maximum tolerated drug levels for each individual patient. This method of dose adaptation is already readily used to decrease the dose of axitinib when intolerable AEs arise but can also be used to inform decisions to increase the dose when they do not. Of these AEs, hypertension has been validated as a clinical parameter that can be used to identify patients eligible for dose escalation, and there is significant evidence that patients who develop hypertension with anti-VEGFR therapies may have better clinical outcomes. In a population PK pooled analysis, logistic regression was performed (using data from patients with mRCC) to evaluate the relationship between RECIST-based ORs and diastolic blood pressure (dBP) [31]. Results demonstrated a strong association ( $p = 0.0042$ ) between change in dBP and the probability of a response (i.e., 1.6-fold increase in the probability of achieving a partial response for every 10 mmHg increase in dBP; Pfizer Ltd, data on file) [31]. A univariate Cox proportional regression was then performed to explore the relationship between dBP and PFS or OS, using dBP as both a categorical and continuous variable. Median PFS was 14.6 months in patients with dBP  $\geq 90$  mmHg versus 7.86 months in patients with dBP  $< 90$  mmHg (HR: 0.590;  $p = 0.006$ ) [31]. Similarly, the median OS was longer in patients with dBP  $\geq 90$  mmHg than in patients with dBP  $< 90$  mmHg (29.5 vs 18.5 months; HR: 0.622;  $p = 0.024$ ) [31]. Although these results are notable, they do not indicate that the absence of hypertension means a patient is not gaining benefit from the drug; indeed, these findings may be another element of interpatient variability. Also, the intent is not to keep the patient in a hypertensive state; once a patient on any anti-VEGFR agent develops an increase in BP, the patient needs to be treated with standard antihypertensive therapy to manage this condition. Therefore, increases in BP during treatment with axitinib may serve as a biomarker for effective drug dosing but should be considered as one parameter of the overall AE assessment and managed accordingly. At present, BP and AEs serve as the only points by which to guide axitinib dosing. However, more individualized approaches to dose titration are currently being explored (see 'Individualizing the axitinib dose – practical guidance' section).

### Axitinib dose individualization in clinical practice

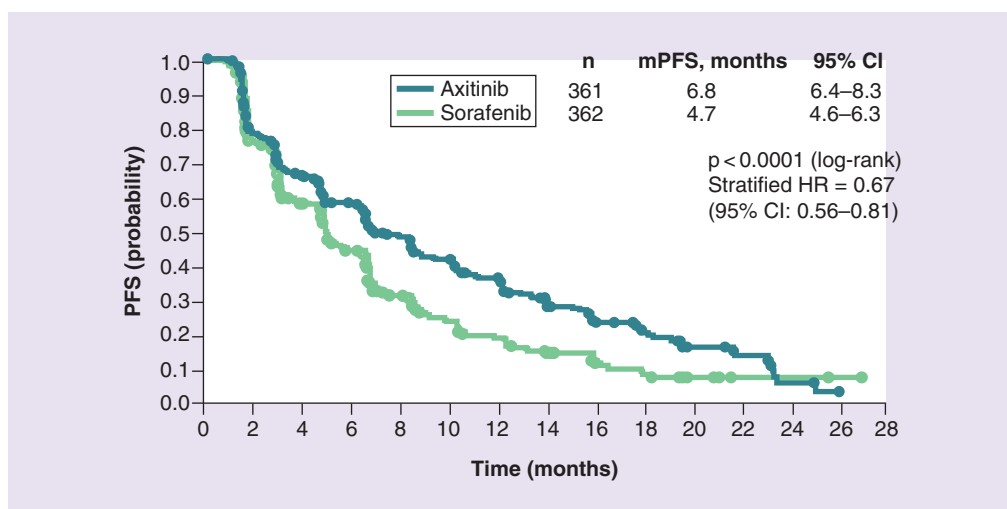
#### The favorable benefit–risk ratio supports individualized dosing

When dosed appropriately, axitinib has a favorable benefit–risk profile; it is a highly potent and selective drug that has a manageable side-effect profile (i.e., potency and selectivity are not achieved at the expense of increased toxicity) and provides meaningful clinical benefit in patients who have progressed on a previous TKI [10].

Axitinib has several distinguishing properties that help to explain its AE profile and to differentiate it from other VEGFR inhibitors. For example, axitinib is a more potent inhibitor of VEGFR-1, -2 and -3 than other approved VEGFR TKIs, with the exception of cabozantinib for VEGFR-2 [38–41]. Potent VEGFR inhibition may improve effectiveness and ease of dose adjustment [38], but does not mean that safety is compromised. Axitinib is also a selective inhibitor of VEGFR-1, -2 and -3 at subnanomolar concentrations *in vitro* [38,39]; its  $IC_{50}$  (the half maximal inhibitory concentration) is tenfold lower for VEGFRs than for other receptors tested [39]. This high selectivity of axitinib for the VEGFRs over other receptor tyrosine kinases means that there are reduced 'off-target' effects that may lead to additional toxicities [42].

With regard to efficacy, in a large, multicenter Phase III study (AXIS) of 723 patients with mRCC [10,13], axitinib significantly improved PFS in the second line compared with sorafenib: median PFS was 6.8 months (95% CI: 6.4–8.3) for axitinib versus 4.7 months (95% CI: 4.6–6.3) for sorafenib (HR: 0.67; 95% CI: 0.56–0.81;  $p < 0.0001$ ; Figure 4) [10,13]. Patients in the AXIS trial who met clinical criteria (i.e., if, after two consecutive weeks, no AEs  $> Grade 2$  and BP  $\leq 150/90$  mmHg and no antihypertension treatment) were encouraged to have their dose escalated [10].

The tolerability of axitinib has been shown to be similar to that of sorafenib, with some differences. Common axitinib-associated AEs, such as diarrhea, hypertension and fatigue, have been reported with other VEGFR inhibitors [10]. Other AEs less commonly reported with axitinib were hand–foot syndrome, cutaneous toxicities and myelosuppression, highlighting one potential advantage of a more specific VEGFR inhibitor [10]. The manageable AE profile in second-line use also allows the flexibility to increase the dose in patients who can tolerate it. Overall, the side-effect profile of axitinib may be more tolerable for some patients and may allow them to remain on therapy



**Figure 4.** Kaplan–Meier curve of progression-free survival of axitinib versus sorafenib by independent assessment for the overall population in a Phase III trial involving patients with relapsed/refractory advanced renal cell carcinoma.

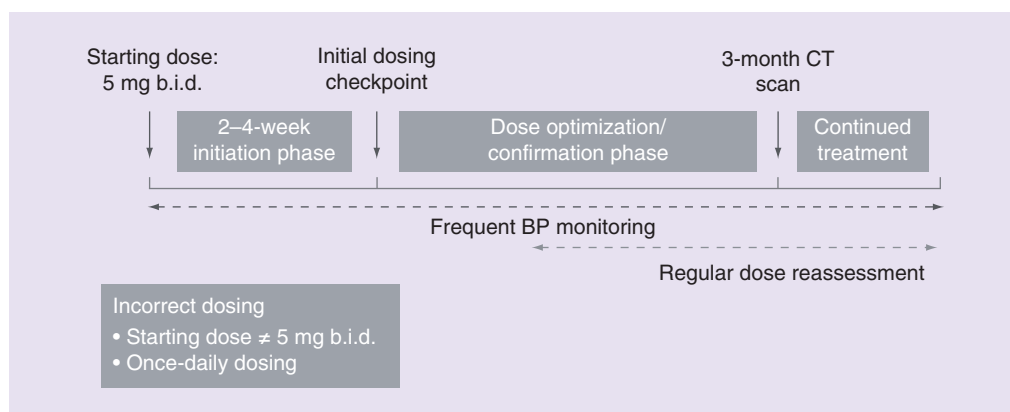
CI: Confidence interval; HR: Hazard ratio; mPFS, Median progression-free survival; PFS: Progression-free survival.

for longer while maintaining clinical benefit [10]. Indeed, data from a pooled analysis of axitinib patients showed declining or stable rates of most AEs over time, supporting acceptable long-term safety [43]. Furthermore, in a *post hoc* analysis of data from the AXIS trial [44], the toxicity profile was similar regardless of the duration of prior sunitinib (i.e., there is no evidence of additive toxicity with use of second-line axitinib with a longer vs shorter duration of first-line TKI use).

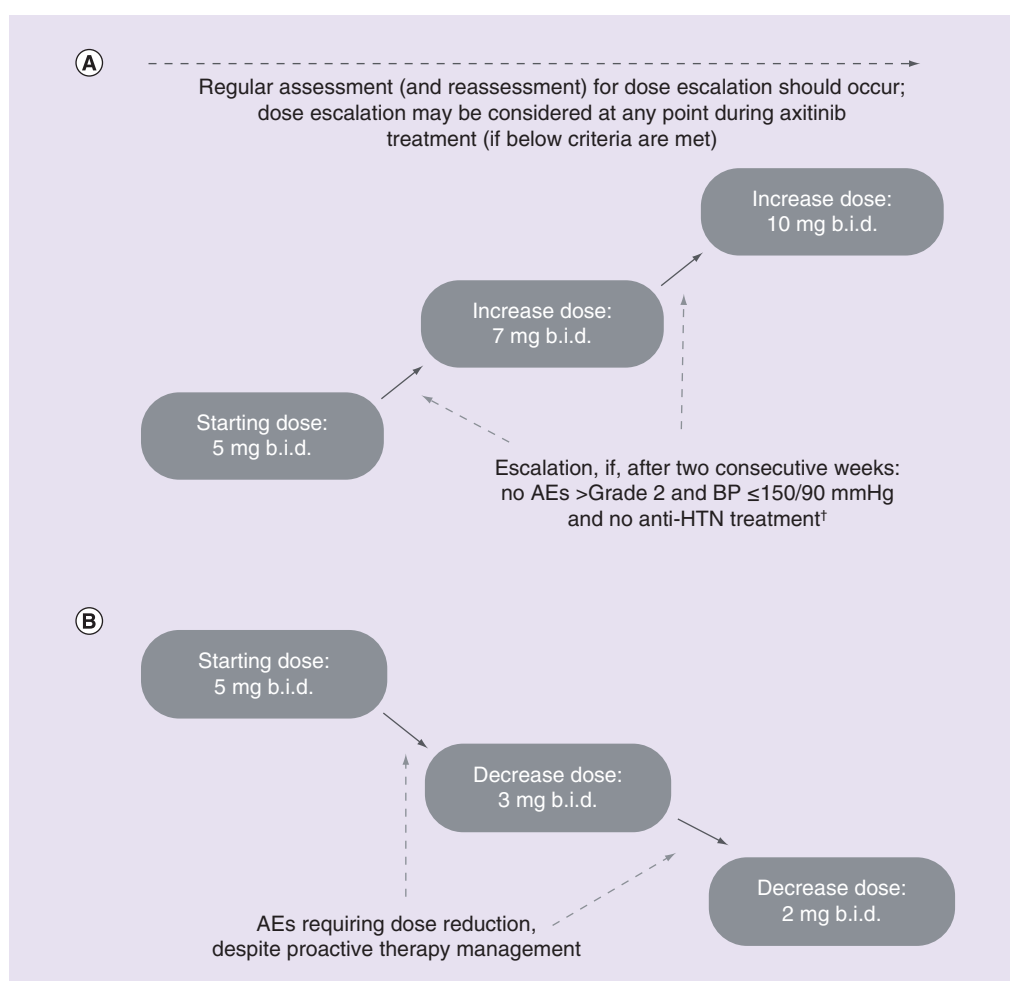
#### Individualizing the axitinib dose – practical guidance

Learnings about interpatient variability and knowledge of other TKIs led to awareness of the need to account for interpatient variability when dosing axitinib. The favorable AE profile of axitinib allows for dose escalation, and the option to dose escalate (based on clinical criteria) was introduced into Phase II and III clinical trials [9,10]. In the AXIS trial [10], approximately the same proportion of patients remained on 5 mg b.i.d., were dose escalated to >5 mg b.i.d. and were dose reduced to <5 mg b.i.d. [45], illustrating that three broader groups of patients exist: those who can tolerate and may benefit from a dose escalation >5 mg b.i.d.; those who have manageable toxicity at 5 mg b.i.d. but are not suitable for a dose escalation; and those who require a dose reduction to <5 mg b.i.d. It is not possible to predict which of these three groups a patient will fall into before starting axitinib therapy, and physicians should not prejudge the patient sitting in front of them. To help guide physicians (and explain this concept to patients so they are aware of the possibility that their initial dose may be modified), a schematic depicting the proposed dose adjustment process may be helpful (Figure 5). This depicts an initial 2–4-week initiation period at 5 mg b.i.d. to assess tolerability. This is followed by a dosing checkpoint at which the physician decides which of the three broader groups a patient fits into so that they can act accordingly (i.e., to keep the patient on 5 mg b.i.d. or to increase/decrease the dose). Further dosing checkpoints should be made at 2–4-week intervals until a steady, tolerated dose is achieved for that individual patient. It is important that the dosing checkpoint is used to assess the correct dose and that dose adjustments are made if required; physicians should not wait until the 3-month CT scan to modify the dose because they risk compromising outcomes for their patients. Guidance regarding the clinical criteria and how to escalate or reduce the dose of axitinib is outlined in Figure 6 [13]. If the patient is experiencing unmanageable AEs, the dose will need to be reduced; however, a dose reduction does not preclude a subsequent re-escalation once AEs have resolved, if appropriate. For some patients, taking a short break (e.g., 2–3 days) before restarting at the reduced dose may help initial toxicities to resolve quickly; the short half-life of axitinib does mean that toxicities usually resolve rapidly after treatment interruption [13,46]. Dose interruption to allow resolution prior to considering dose reduction may be particularly helpful for severe or unmanageable toxicities. Dose interruptions (owing to missed dose or toxicity) were reported in >75% of all treated patients (axitinib or sorafenib) in the AXIS trial [10]. If the patient receives axitinib 10 mg b.i.d. without experiencing elevated BP or other dose-related AEs,





**Figure 5. Individualizing the dose for every patient.**  
b.i.d.: Twice-daily; BP: Blood pressure.



**Figure 6. Clinical criteria for axitinib dose adjustment. (A)** Criteria for increasing or **(B)** decreasing the axitinib dose, dependent on individual safety and tolerability (according to the label).

†Dose escalation is currently not recommended if a patient is already hypertensive/taking antihypertensive medication according to the axitinib summary of product characteristics [13], but frequently occurs (with appropriate monitoring and treatment) in real-world clinical practice.

AE: Adverse event; b.i.d.: Twice-daily; BP: Blood pressure; HTN: Hypertension.

treatment should be maintained at this dose; escalating the dose beyond 10 mg b.i.d. should be avoided because of a lack of supportive data [13].

Alternative schema may highlight other methods to optimize axitinib dose but require further study [47,48]. Most recently, as part of an ongoing Phase II trial of axitinib for mRCC after PD-1/PD-L1 inhibition (www.clinicaltrials.gov, NCT02579811), patients receive axitinib 5 mg b.i.d. with the dose increased in 1 mg b.i.d. increments every 14 days if no Grade 2 axitinib-related AEs are observed. Rather than immediately reducing the dose for Grade 2 AEs, patients will undergo a brief treatment break and resume with the same dose if AE severity falls below Grade 2. Doses will be reduced (in 1 mg b.i.d. increments) in patients with recurrent Grade 2 AEs despite treatment break, and per physician discretion. In this way the dose intensity of axitinib can be maximized while AEs are kept at a manageable level.

### Proactive management of AEs

Although some patients will require a dose reduction because of AEs, it is important that AEs are, in the first instance, managed proactively [46]. During axitinib treatment, patients should be closely monitored for the development of AEs, which should be treated promptly and in line with standard medical interventions [39,49–50]. The physician's role is to provide maximum benefit from axitinib by proactively managing both the dose and any toxicities that may arise. Although toxicity may increase with increased dose, safety concerns should not prohibit dose escalation in patients who meet the clinical eligibility criteria. In the AXIS study, treatment-related AEs and Grade  $\geq 3$  treatment-related AEs in the axitinib arm were similar in dose-escalated (90.2 and 50.0%, respectively) and non-escalated (90.7 and 48.9%, respectively) patients [51]. Patients should also be educated about the potential occurrence of side effects and how to recognize and manage them as soon as they arise [46], particularly in the case of common AEs such as diarrhea, fatigue/asthenia, dysphonia and hypertension. For example, diarrhea can be managed through dietary modifications and concomitant antidiarrheal medication, fatigue/asthenia managed through energy-conserving strategies and dysphonia through ample water intake and avoidance of irritants such as tobacco smoke [46]. It is important that BP is under control before treatment initiation and is frequently monitored during axitinib treatment, and that the importance of hypertension is clearly communicated to patients.

Appropriate management of hypertension, if it arises, is essential. If antihypertensive agents are required to control high BP, treatment guidance (e.g., European Society of Cardiology guidelines) [52] should be followed. However, angiotensin system inhibitors may now be the treatment of choice, following analyses of data from Izzedine *et al.* [53] and McKay *et al.* [54] showing that concomitant use of angiotensin system inhibitors is associated with significant improvements in survival outcomes in patients with mRCC. Dose escalation is currently not recommended if a patient is already hypertensive/taking antihypertensive medication according to the axitinib summary of product characteristics [13], but frequently occurs (with appropriate monitoring and treatment) in real-world clinical practice.

### Conclusion

Compared with other approved VEGFR TKIs, axitinib is a highly potent and selective VEGFR inhibitor; it is these properties that contribute to the effectiveness of axitinib without compromising its safety profile. However, achieving maximum benefit from axitinib may be hindered in certain patients by inappropriate individual dosing. There are a number of factors that may contribute to this, including incorrect once-daily dosing (the short half-life of axitinib means that therapeutic levels are only maintained by b.i.d. dosing) or initiating treatment below the appropriate starting dose of axitinib of 5 mg b.i.d. Once a patient has been initiated on the 5 mg b.i.d. starting dose, further dose modifications may be required because this nonindividualized fixed dose of axitinib does not take into account interpatient variability, which has been demonstrated not only for axitinib but for all oral mRCC drugs. Clinical studies have shown that after initiation of axitinib at 5 mg b.i.d., three broader groups of patients exist: those who can tolerate and may benefit from a dose escalation  $> 5$  mg b.i.d.; those who have manageable toxicity at 5 mg b.i.d. but are not suitable for a dose escalation; and those who require a dose reduction to  $< 5$  mg b.i.d. Therefore, it is important to use clinical criteria to assess which group a patient falls into and to follow practical guidance regarding individualized treatment. By following this guidance, physicians can reach the full potential of axitinib and optimize outcomes for their patients, without compromising safety. Proactive management of AEs is a key part of overall therapy management with any oncology drug, and educating patients on what toxicities may occur is part of this process. If toxicities do arise, the short half-life of axitinib usually allows them to resolve rapidly after a short break in treatment.

## Future perspective

New agents have recently been approved for the management of patients who have previously failed to respond to first-line TKIs. Nivolumab, a checkpoint inhibitor that restores T-cell function, has demonstrated statistically significant and clinically meaningful OS and ORR benefit when compared with everolimus [55]. Cabozantinib, a new generation oral TKI that targets MET, AXL and VEGFR, has also shown a statistically significant benefit in three efficacy endpoints (ORR, PFS and OS) versus everolimus [56]. Both agents have enriched the armamentarium for renal cell carcinoma treatment in second-line.

In the future, axitinib may come to play a major role in first-line. Based on a synergism between checkpoint inhibitors with some TKIs, the concept of combining these two strategies was investigated in Phase I trials. The combination of a potent and selective VEGFR inhibitor (such as axitinib) with a checkpoint inhibitor (avelumab or pembrolizumab) proved to be feasible in terms of safety. Moreover, initial efficacy data were highly promising with response rates up to 75% [57,58].

## Executive summary

### Rationale for individualized dosing

- Axitinib is a potent, selective, second-generation VEGFR inhibitor for the second-line treatment of metastatic renal cell carcinoma.
- Individualized dosing, accounting for interpatient variability, is the preferred approach to optimize efficacy, while minimizing adverse effects.

### How the dosing schedule & starting dose of axitinib were determined

- Axitinib has a half-life of 2.5–6.1 h and reaches a steady state within 2–3 days of the initial dose, maintained by twice-daily (b.i.d.) dosing.
- The recommended dose of axitinib is 5 mg b.i.d., as confirmed in AXIS.

### Interpatient variability in axitinib exposure

- Various factors, including the absorption, distribution, metabolism, elimination, drug–drug interactions, genetic variations and patient compliance, all affect drug exposure and contribute to interpatient variability.
- Pharmacokinetic data confirm that dose escalation increases drug exposure in patients who are able to tolerate it.

### Interpatient variability in drug exposure translates into variability in efficacy

- Clinical trials have demonstrated significant associations between axitinib exposure and efficacy outcomes, leading to a 1.5-fold increase in the probability of achieving a partial response for every 100 ng·h/ml increase in area under the concentration–time curve (AUC).
- In patients with  $AUC \geq 300$  ng·h/ml, median progression-free survival and overall survival were found to be significantly longer compared with those with  $AUC < 300$  ng·h/ml, and results were even more significant when AUC was assessed as a continuous variable.
- Dose escalation of axitinib also resulted in a significant improvement in drug exposure, with a positive trend toward improvement in overall survival.

### How can we address interpatient variability?

- Therapeutic drug monitoring and phenotype-/genotype-guided dosing are two methods that can be used to address interpatient variability but are currently not feasible for use with axitinib.
- Toxicity-adjusted dosing can be used for axitinib based on adverse events, of which hypertension has been validated as a clinical parameter to identify patients eligible for dose escalation.

### Axitinib dose individualization in clinical practice

- Axitinib has been shown to have a favorable benefit–risk profile due to its high selectivity and potency with good tolerability, supporting individualized dosing.
- Axitinib is recommended to be initiated at 5 mg b.i.d. for 2–4 weeks, followed by a dosing checkpoint to identify the need for dose adjustment, with further dosing checkpoints every 2–4 weeks until a steady, tolerated dose is achieved.
- Adverse effects should be managed proactively, according to treatment guidance, and patients should be educated regarding possible toxicities that could arise.

### Conclusion

- Axitinib is a highly potent and selective VEGFR inhibitor, which contributes to its effectiveness and good safety profile.
- Interpatient variability should be taken into account to optimize clinical outcomes without compromising safety, based on clinical criteria to identify patients that would benefit from dose escalation, reduction or those that are not suitable for dose escalation.
- Proactive management of adverse events and appropriate patient education are also essential elements of therapeutic management.

Based on these findings, the combination of axitinib and avelumab is being explored in a randomized Phase III trial versus sunitinib (JAVELIN RENAL 101; NCT02684006), as well as in combination with pembrolizumab (KEYNOTE-426; NCT02853331). In this context, the dosing flexibility of axitinib may be valuable in exploiting the synergy of the combination, since lower doses of anti-angiogenic agents may be more effective than conventional doses and also positively impact the efficacy/safety ratio [59].

#### Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: [www.futuremedicine.com/doi/suppl/10.2217/fon-2017-0455](http://www.futuremedicine.com/doi/suppl/10.2217/fon-2017-0455).

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